Cardiovascular Implications of Hypoglycemia in Diabetes Mellitus

Kim A. Connelly, MBBS, PhD; Andrew T. Yan, MD; Lawrence A. Leiter, MD; Deepak L. Bhatt, MD, MPH; Subodh Verma, MD, PhD

Case presentation: An 81-year-old man presents to the physician’s office for a routine review. He has had a previous myocardial infarction treated with percutaneous coronary intervention, and has a history of hypertension, dyslipidemia, and type 2 diabetes mellitus complicated by stage 3a chronic kidney disease. Medical therapy includes aspirin, clopidogrel, metformin 1000 mg twice daily, a sulfonylurea, ramipril 10 mg daily, amlodipine 10 mg daily, metoprolol 50 mg twice daily, and atorvastatin 80 mg daily. He is asymptomatic following his percutaneous coronary intervention, with no evidence of heart failure. His left ventricular systolic function on the last echocardiogram was normal.

He describes frequent episodes of shakiness and unsteadiness, in combination with a low capillary glucose reading (59 mg/dL [3.3 mmol/L]), especially after a delayed meal. His hemoglobin A1c (HbA1c) is 6.9% with an estimated glomerular filtration rate of 49 mL/min. He had 1 episode of hypoglycemia requiring assistance by a friend. He did not see his family doctor, but states it was a frightening experience and he was afraid to continue taking his medications. His quality of life has also suffered, because he is not confident to drive his vehicle and is afraid he will lose his license.

Introduction

Diabetes mellitus represents a global epidemic, with the International Diabetes Federation projecting that the prevalence of diabetes mellitus will reach 592 million people by 2035.1 A substantial proportion of patients with diabetes mellitus will die of a cardiovascular cause, with overall life expectancy being reduced by ≈7.5 years in men and 8.2 years in women.2 Furthermore, diabetes mellitus is complicated by substantial morbidity, not only as a result of microvascular complications, including retinopathy, nephropathy, peripheral and autonomic neuropathy, but also because treatment-related hypoglycemia itself poses a significant risk. Indeed, the national diabetes statistics report showed that in 2011, ≈282 000 emergency department visits for adults aged ≥18 years had hypoglycemia as the first-listed diagnosis and diabetes mellitus as another diagnosis. Furthermore, recent trends among Medicare beneficiaries in US hospitals show that admissions for hypoglycemia now exceed those for hyperglycemia. The significance of this clinical problem cannot be overstated.

The American Diabetes Association describes 5 categories of hypoglycemia: severe hypoglycemia (requiring aid of another person to administer treatment), documented symptomatic hypoglycemia (common hypoglycemic symptoms and measured plasma glucose of ≤70 mg/dL [3.9 mmol/L]), asymptomatic hypoglycemia (not accompanied by symptoms but a glucose measurement of ≤70 mg/dL [3.9 mmol/L]), probable symptomatic hypoglycemia (self-reported symptomatic episode not...
verifies by glucose determination), and relative hypoglycemia (symptoms associated with plasma glucose >70 mg/dL (3.9 mmol/L)). Importantly, the severity of hypoglycemia is defined by the clinical manifestations rather than by the actual glucose level (Table 1), with mild hypoglycemia typically exemplified by mild autonomic symptoms, and the ability of the patient to self-treat. Severe hypoglycemia often requires the intravenous administration of glucose or subcutaneous glucagon, or the oral administration of carbohydrates. It typically occurs when plasma glucose is ≤50 mg/dL (≤2.8 mmol/L).

Hypoglycemia in patients with type 2 diabetes mellitus is a frequent event. Severe hypoglycemia has been shown to occur at rates of 35 to 70 episodes per 100 patient-years. More recent trials such as the Veterans Affairs Diabetes Trial (VADT), the Action to Control the Cardiovascular Risks in Diabetes (ACCORD) trial, and the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial demonstrated that intensive glucose control was associated with a significant increase in the risk of severe hypoglycemia (Table 2).

The true incidence of mild hypoglycemia is more difficult to assess, because most trials have relied on self-reported episodes. However, with the use of continuous glucose monitoring in patients with type 2 diabetes mellitus, the incidence of unrecognized hypoglycemia has been reported to be as high as 46% (81 episodes in 39 patients over a 3-day period), with ≈43% of episodes being nocturnal.

### Risk Factors for the Development of Hypoglycemia

Hypoglycemia is most commonly associated with the use of insulin secretagogues (primarily sulfonylureas) or insulin. Other risk factors include advanced age and cognitive impairment, renal dysfunction, duration of diabetes mellitus, and missed or irregular meals (Table 3). Furthermore, impaired awareness of hypoglycemia symptoms remains a risk factor. Indeed, Bremer and colleagues demonstrated that in patients 65 years of age with type 2 diabetes mellitus, there was a marked subjective unawareness of hypoglycemia. Importantly, this did not depend on altered neuroendocrine counterregulation, and thus may contribute to the increased probability of severe hypoglycemia. The risk factors for nonsevere versus severe hypoglycemia also vary. For example, a detailed analysis of the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial demonstrated that nonsevere hypoglycemic episodes were independently associated with younger age, lower body mass index, the presence of diabetes mellitus at study enrollment, and higher baseline HbA1c level, whereas severe hypoglycemia episodes were associated with older age, hypertension, higher serum creatinine level, and lower cognitive function, but not baseline glycemic status.

### Clinical Outcomes in Patients With Severe Hypoglycemia

Although the exact cause for adverse events in patients with severe hypoglycemia is not known, there is a clear association between severe hypoglycemia and adverse outcomes, including cardiovascular mortality and all-cause mortality. Indeed, a consistent feature of recent large outcome trials is the association of >1 severe hypoglycemic episode with increased mortality. For instance, severe hypoglycemia is associated with >4-fold higher cardiovascular mortality in VADT and a >2.8% mortality rate per year in ACCORD; the hazard ratio for cardiovascular mortality was 3.79 in ADVANCE. Indeed, the significance of these findings led to the 2013 recommendation from the American Diabetes Association that “less stringent HbA1c targets” may be appropriate for those patients with a history of severe hypoglycemia, advanced microvascular or macrovascular complications, or extensive comorbid conditions.

Although the excess mortality might be attributed to the hypoglycemia itself, the data are conflicting. For instance, Gerstein et al present an analysis of the ACCORD trial that demonstrates a paradoxical association between standard therapy, 1 episode of severe hypoglycemia, and increased mortality, whereas more frequent episodes of hypoglycemia in the intensively treated arm had lower mortality. In addition, an analysis of the ADVANCE trial revealed that the participants with a history of severe hypoglycemia had an increased risk for not just cardiovascular, but also nonvascular outcomes (including respiratory, digestive, and skin conditions).

### Table 2. Rates of Hypoglycemia in the ACCORD, VADT, and ADVANCE Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>Standard Arm, %</th>
<th>Intensive Arm, %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCORD</td>
<td>5.1</td>
<td>16.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>1.5</td>
<td>2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VADT</td>
<td>9.9</td>
<td>21.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Table 3. Risk Factors for Severe Hypoglycemia

- Hemoglobin A1c <6%
- Hypoglycemic unawareness
- Autonomic neuropathy
- Cognitive impairment
- Renal dysfunction
- Insulin therapy
- Sulfonylurea therapy
- Previous episodes of severe hypoglycemia
- Missed meals
suggesting that hypoglycemia may be a marker of a vulnerable patient rather than causative. These seemingly paradoxical observations underscore the complexity of the interaction between severe hypoglycemia and pharmacological therapy and the impact on mortality.

Possible Cardiovascular Consequences of Severe Hypoglycemia

The association between adverse cardiovascular outcomes and severe hypoglycemia is not well understood. There is, however, a growing body of evidence of potential mechanisms linking hypoglycemia to the development of adverse cardiovascular outcomes. Hypoglycemia itself has been shown to negatively impact various pathways that might promote cardiovascular disease. These include, but are not limited to:

1. blood coagulation abnormalities
2. inflammation
3. endothelial dysfunction
4. sympathetic nervous system activation

Blood Coagulation Abnormalities

Hypoglycemia is known to influence platelet aggregability and alter several components of the inflammatory cascade. Indeed, hypoglycemia dramatically increases P-selectin expression (a marker of platelet activation), fibrinogen, and factor VIII levels, along with a reduction in plasminogen activator inhibitor-1 in studies of subjects with type 1 diabetes mellitus. Reduced systemic fibrinolytic balance and enhanced platelet-monocyte aggregation provide a biological rationale for the increased rates of acute ischemic events seen in patients with diabetes mellitus and hypoglycemia. Similarly, subjects with type 2 diabetes mellitus demonstrate greater platelet aggregation despite treatment with aspirin and adenosine diphosphate receptor antagonists than their counterparts without diabetes mellitus.

Inflammation

Akin to changes seen in the blood coagulation cascade, hypoglycemia has also been demonstrated to increase circulating inflammatory markers such as CD40, CD40 ligand, interleukin-6, high-sensitivity C-reactive protein, oxidative stress, and other proinflammatory and atherothrombotic biomarkers such as vascular adhesion molecules vascular cell adhesion molecule 1, intercellular adhesion molecule 1, and E-selectin, vascular endothelial growth factor, along with tumor necrosis factor-α. However, in a cohort of 1066 subjects with type 2 diabetes mellitus, although severe hypoglycemia was associated with a significant increase in the odds of experiencing a macrovascular event, elevated proinflammatory markers were not predictive of subsequent events over a 4-year period. Again, these findings underscore the complexity of the interaction between hypoglycemia and cardiovascular events.

Endothelial Dysfunction

A wealth of evidence clearly demonstrates that abnormal endothelial function remains an early marker of subclinical atherosclerosis, and that subjects with type 2 diabetes mellitus demonstrate altered endothelial-dependent and -independent responses. The direct effects of hypoglycemia on endothelial function are less well established. Sommerfield et al show in a cohort of subjects with type 1 diabetes mellitus that hypoglycemia resulted in a reduction in arterial wall stiffness and augmentation index, probably as a result insulin-induced changes in the arterial endothelium. Although this in isolation may not represent a major risk factor for cardiovascular disease, hypoglycemia-induced endothelial dysfunction may act in concert with inflammatory biomarkers and blood coagulation abnormalities to promote cardiovascular events.

Sympathoadrenal Responses

The well-documented sympathetic response to hypoglycemia represents a counterregulatory mechanism to diminish the impact of abnormally low glucose levels. The release of catecholamines has profound effects on the cardiovascular system, directly altering cardiac contractility, myocardial work, cardiac output, and therefore oxygen demand. This may induce ischemia in subjects with preexisting coronary artery disease. Catecholamine excess also has direct effects on platelet reactivity and may potentially be proarrhythmic. For instance, hypoglycemia has been shown to significantly prolong the QT interval, which was an independent predictor of mortality in the MONICA/KORA Augsburg study. Stahn et al also demonstrated a significant relationship between asymptomatic hypoglycemic episodes and ventricular extrasystoles/nonsustained ventricular tachycardia. Furthermore, antecedent hypoglycemia may impair autonomic function, leading to reduced heart rate variability – an independent predictor of poor outcomes in the population with diabetes mellitus. Catecholamine excess may also induce hypokalemia and increase intracellular Ca²⁺. This can result in delayed afterdepolarizations, along with the prolongation of action potentials by blockade of current through the human ether-a-go-go–related gene (hERG) potassium channel, all of which have been implicated in the development of lethal cardiac arrhythmias.

Novel Oral Antihyperglycemic Agents and Hypoglycemia

The past decade has seen the development of multiple antihyperglycemic agents. Although side effects such as heart failure, weight gain, and bone fractures have limited the use of thiazolidinediones, a number of new classes of drugs are available that have been widely adopted to improve glycemic control. Two distinct drug classes exist that modify glucagon-like peptide-1 (GLP-1) – collectively referred to as the “incretins.” These agents potentiate the incretin effect either through direct receptor ligand binding (achieved by the injectable GLP-1
receptor agonists) or via inhibition of the enzyme responsible for degradation of GLP-1, dipeptidyl peptidase 4 (the DPP-4 inhibitors). The second class of agents improves glycemic control by enhancing urinary glucose excretion via inhibition of the sodium-glucose cotransporter 2 (SGLT2) in the kidney (SGLT2 inhibitors). In comparison with sulfonylureas, meglitinides, or insulin, the GLP-1-receptor agonists, DPP-4 inhibitors, and SGLT2 inhibitors all demonstrate a substantially reduced rate of hypoglycemia (Table 4) and are effective in improving glycemic control.

Newer pharmacological therapies have a significantly reduced the rate of severe hypoglycemic episodes. In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 (SAVOR-TIMI 53) trial, which assessed cardiovascular outcomes in patients with type 2 diabetes mellitus and cardiovascular risk factors, there was a significantly increased risk of symptomatic hypoglycemia in the saxagliptin group in comparison with the placebo group. However, a subsequent analysis demonstrated that this risk was only seen in those patients taking a combination of a sulfonylurea and the DPP-4 inhibitor saxagliptin, especially in those with a baseline HbA1c of <7%. Importantly, DPP-4 inhibitor therapy alone, or combination therapy for subjects with a baseline HbA1c >7%, did not increase this risk. The low rate of hypoglycemia induced by DPP-4 inhibitors was also seen in the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial, where 5380 patients with type 2 diabetes mellitus and an acute coronary syndrome requiring hospitalization within the previous 15 to 90 days were randomly assigned to receive alogliptin or placebo in addition to existing anti-hyperglycemic and cardiovascular drug therapy. Like SAVOR-TIMI 53, this trial demonstrated neutral effects in regard to cardiovascular outcomes, although no increase in hypoglycemia episodes was observed. There was also an increase in hospitalization for heart failure noted in both trials (not statistically significant in EXAMINE, potentially because of limited statistical power), although no clear mechanism was identified. Over the next 5 years, a number of other large outcome trials will be reported for both GLP-1 receptor agonists and DPP-4 inhibitors, which will clarify their role in the management of diabetes mellitus, and provide further data regarding hypoglycemia (and heart failure and other end points, as well).

With respect to SGLT2 inhibitors, an interim analysis of the Canagliflozin Cardiovascular Assessment Study (CANVAS) trial using canagliflozin has reported overall neutral cardiovascular outcomes, with the trial expected to complete with final outcomes in 2017/2018. Other SGLT2 inhibitors such as empagliflozin and dapagliflozin are also under investigation to demonstrate cardiovascular safety, with the EMPA-REG OUTCOMES and DECLARE-TIMI 58 trials hopefully reporting in 2015 and 2019, respectively. SGLT2 inhibitors demonstrate a significantly lower rate of hypoglycemia in comparison with sulfonylurea drugs, with an ≈10-fold reduction in hypoglycemic episodes. Other effects include weight loss, diuresis, and a reduction in systolic blood pressure, all of which may be beneficial.

**Recommendations for Clinicians**

The following recommendations/suggestions are offered to the clinician treating a patient with glucose-lowering therapies:

1. Recognize that hypoglycemia is exceedingly common, and that this is usually attributable to sulfonylurea and insulin therapy. Renal dysfunction and older age are also important risk factors for hypoglycemia.

2. Recognize that hypoglycemia is a cause of significant fear and morbidity, and has a negative impact on the quality of life for patients with diabetes mellitus.

3. Recognize that episodes of severe hypoglycemia are associated with increased all-cause and cardiovascular mortality in patients with type 2 diabetes mellitus. Various proinflammatory, thrombotic, proatherosclerotic, and proarrhythmogenic processes have been suggested as potential mediators for the adverse effects of hypoglycemia on the heart.

4. Recognize that newer glucose-lowering agents such as the incretin (GLP-1 receptor agonists and DPP-4 inhibitors) and SGLT2 inhibitor classes of agents are associated with much lower rates of hypoglycemia relative to sulfonylureas or insulin, and may be considered as preferred add-on therapies to metformin in patients with diabetes mellitus.

5. Appreciate that all new anti-hyperglycemic therapies being evaluated in clinical trials have to meet strict Food and Drug Administration noninferiority criteria for cardiovascular safety. Thus far, 2 trials with DPP-4 inhibitors (saxagliptin and

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### Table 4. Rates of Hypoglycemia and Change in HbA1c With Current Antihyperglycemic Agents

<table>
<thead>
<tr>
<th>Change in HbA1c, %</th>
<th>Hypoglycemia, %</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>−0.82*</td>
<td>8.86*</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>−0.71*</td>
<td>10.51*</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>−0.69*</td>
<td>1.13</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>−1.02*</td>
<td>0.92</td>
</tr>
<tr>
<td>Basal insulin</td>
<td>−0.88*</td>
<td>4.77*</td>
</tr>
<tr>
<td>Premixed insulin</td>
<td>−1.07*</td>
<td>17.78*</td>
</tr>
</tbody>
</table>

DPP-4 indicates dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; and HbA1c, hemoglobin A1c.

*Significant versus placebo.

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alogliptin) have demonstrated a reasonable degree of cardiovascular safety as per the Food and Drug Administration criteria of noninferiority.

**Back to the Patient**

The patient in question had 1 episode of severe hypoglycemia, and has multiple risk factors (age, renal dysfunction, sulfonylurea usage) for the development of future episodes. Furthermore, not only does the episode of severe hypoglycemia place him at risk for subsequent events with excess mortality, he has developed anxiety and fear over future events, which is highly prevalent in subjects who have experienced episodes of hypoglycemia. His family physician had a long discussion with the patient and a decision was made to cease the sulfonylurea and to commence therapy with a DPP-4 inhibitor, because his physician was concerned regarding the potential for prolonged episodes of severe hypoglycemia with a sulfonylurea.

**Conclusion**

Severe hypoglycemia represents a common and challenging issue in the optimal management of diabetes mellitus. There is an association between severe hypoglycemia and adverse outcomes, but the pathophysiology and direct causal relationships linking diabetes mellitus, pharmacological therapy, and adverse outcomes remain to be elucidated. Novel therapies have demonstrated lower rates of hypoglycemia and, to date, neutral cardiovascular effects. The next 5 to 6 years will see a wealth of data of additional outcome trials that will guide the proper use of second-line glucose-lowering agents to prevent microvascular disease, with neutral or even salutary effects on macrovascular disease, without the risk for adverse effects such as hypoglycemia.

During the review process, the primary results of 3 cardiovascular outcome trials in diabetes mellitus were published. The TECOS study and ELIXA studies demonstrated that the DPP-4 inhibitor sitagliptin and the GLP-1 receptor antagonist lixisenatide, respectively, were non-inferior to placebo and met the US Food and Drug Administration criteria of safety with respect to a composite cardiovascular outcome with no excess in rates of heart failure hospitalizations. The EMPA-REG OUTCOME study reported safety and superiority of the SGLT2 inhibitor empagliflozin in individuals with type 2 diabetes mellitus and cardiovascular disease, accompanied by a marked reduction in cardiovascular and all-cause mortality.

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